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Necrotising soft tissue infections

CLINICAL REVIEW

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Necrotising soft tissue infections can affect the skin, subcutaneous tissue, superficial fascia, deep fascia and musculature. The infections are severe, they spread quickly and can result in extensive tissue loss. Although rare, morbidity and mortality rates are high. Early clinical identification is crucial for the outcome, and rapid infection control through surgery and targeted antibiotic treatment is needed to save lives. Few prospective clinical trials have been conducted for the treatment of this type of infection. Specific challenges include rapid identification of the

condition and the uncertain efficacy of the various treatment options. In this clinical review article, we describe clinical characteristics, diagnostics and treatment.

Necrotising soft tissue infections (NSTIs) are rare, and there is a need for unambiguous diagnostic criteria and nomenclature. The infrequency of the condition makes it challenging to develop and maintain sufficient clinical expertise in this area.

NSTI is a topical issue. The incidence of invasive infections with *Streptococcus pyogenes* (group A Streptococcus), including life-threatening soft tissue infections, is increasing in a number of countries, and several deaths were recorded in Norway in 2023 (1). Based on extensive clinical experience, literature searches and research in the field, we summarise the characteristics of the condition and key aspects of diagnostics and treatment.

Epidemiology and aetiology

Historically, NSTIs have been categorised in different ways: by anatomical location (Ludwig's angina in the mouth, jaw and neck, Fournier's gangrene in the genitals), depth of infection (necrotising cellulitis, fasciitis or myositis) or in terms of microbial aetiology (2). This makes it difficult to compare epidemiological and clinical characteristics across different time periods and geographical contexts.

The incidence is low in Scandinavia, but some studies indicate that it is increasing, with an incidence of 2–5 per 100 000 persons/year (3). The median age is around 60 years, and the majority of cases are men (3–5).

The most common microbial aetiology is summarised in Table 1 (6). Infections are often categorised into type 1 and type 2. Type 1 consists of polymicrobial infections and accounts for 45–85 % of cases. Type 2 consists of monomicrobial infections, where *S. pyogenes* is by far the most common microbe, accounting for up to 60 % of all cases (4, 5). *Streptococcus dysgalactiae*, *Clostridium* spp. and *Staphylococcus aureus* are the cause of most other monomicrobial cases in Scandinavia. *Vibrio vulnificus*, *Aeromonas* spp. and *Shewanella* spp. are rare in Norway but have become relevant due to their association with water exposure and increased water temperatures as a result of climate change.

Table 1

Categorisation of NSTIs by microbial aetiology (6)

Category	Type 1	Type 2
Aetiology	Polymicrobial infections with anaerobic microbes	Monomicrobial infections

Category	Type 1	Type 2
Species	*Bacteroides* spp. *Prevotella* spp. *Fusobacterium* spp. *Clostridium* spp. *Streptococcus viridans* *Streptococcus dysgalactiae* *Staphylococcus aureus* *E. coli/Klebsiella* spp. *Enterococcus* spp.	*Streptococcus pyogenes* *Streptococcus dysgalactiae* *Staphylococcus aureus* *Clostridium* spp. *Vibrio vulnificus* *Aeromonas* spp. *Shewanella* spp.

NSTIs can affect all parts of the body (Figure 1) (4, 6, 7). Approximately 1/3 of cases originate in the abdominal and anogenital regions, 1/3 in the lower extremities, 1/6 in the upper extremities and 1/6 in the head and neck region (4). The authors participated in the INFECT study, which is the largest prospective study on NSTIs to date. The study has shown a clear correlation between anatomical location and probable microbial aetiology (4, 8).

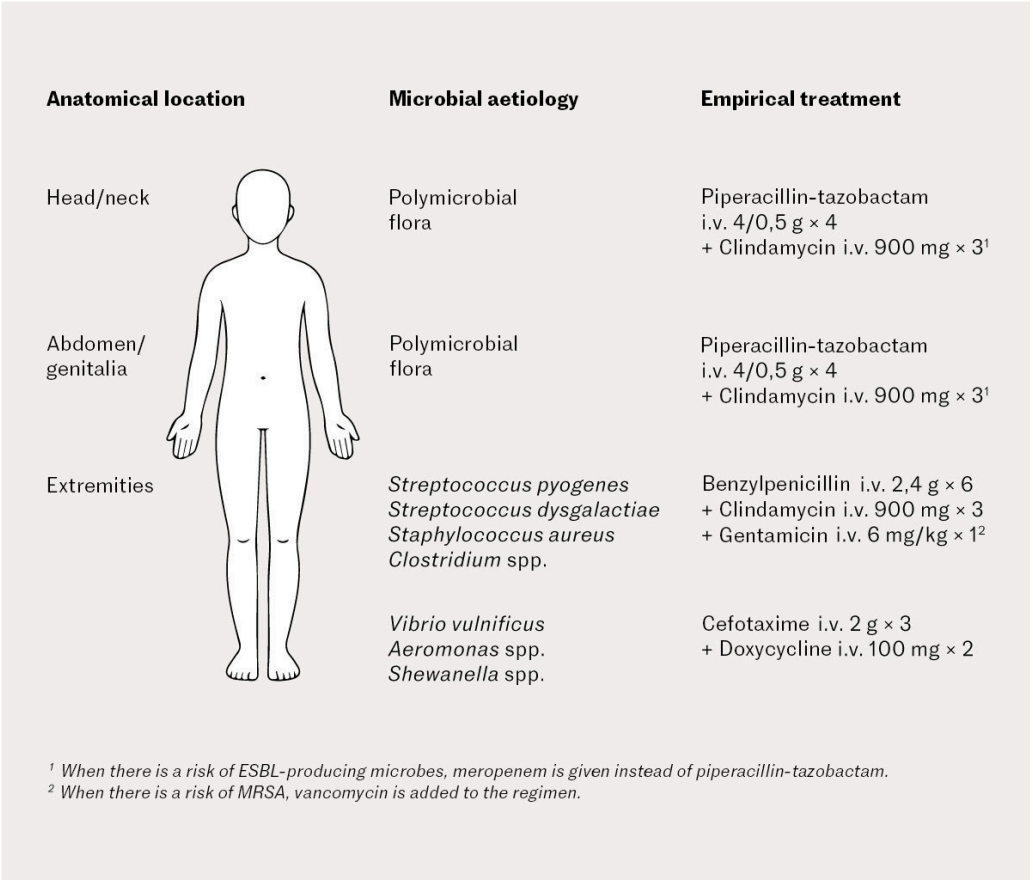

Figure 1 Associations between body part involved, most common microbial findings and recommended empirical antibiotic treatment according to the guidelines (4, 6, 7). i.v. = intravenously.

S. pyogenes and other streptococcal species were predominant in cases involving the extremities, while infections in the abdomen and head and neck region were mainly polymicrobial. A more practical categorisation, based on the association between microbial aetiology and anatomical location, has direct implications for the choice of antibiotic treatment. This is reflected in the Norwegian guidelines for antibiotic treatment (Figure 1) (4, 6, 7).

Pathogenesis

The pathophysiology is complex and differs for monomicrobial and polymicrobial infections (4, 5, 9–12). The microbes can spread haematogenously or via breaches in the skin or mucous membrane barrier. Infections that originate in the skin surface can spread both deeper and outward. Infections can also originate in deeper tissues and spread towards the skin surface. A key aspect of the pathogenesis is thrombus formation in the microcirculation, leading to ischemic necrosis.

The pathogenesis is best described for monomicrobial infections caused by *S. pyogenes*. This bacterial species has virulence factors that promote adhesion, tissue invasion and systemic toxicity, and protect the microbe from host immunity, including biofilm formation in soft tissues. The distinct virulence properties of *S. pyogenes* are borne out by the presence of NSTIs in young people with no known risk factors (10).

The pathophysiology of polymicrobial infections is less well understood. The microbes tend to belong to the patient's normal flora and spread to soft tissues through breaches in the skin or mucous membrane barrier, abscess ruptures or fistulas from non-sterile areas. Polymicrobial infections develop through a complex interaction between microbes in distinct microbiological communities, where the composition of species is not random. These infections typically occur in patients with risk factors such as cardiovascular disease, diabetes mellitus, recent surgery, chronic renal failure, hepatic disease, intravenous drug use, cancer and immunosuppression, but up to 25 % of patients have no known comorbidity (3, 5, 13, 14).

Symptoms and findings

The clinical manifestation of NSTIs varies depending on location, aetiology, duration of symptoms and host factors. There are no pathognomonic symptoms or signs in the early phase. Chronic wounds, recent surgery, penetrating or blunt trauma before symptom onset are common, but many patients report no known preceding event (4, 10). Some patients report flu-like body aches prior to admission, and fever is common. Typical signs of inflammation, such as erythema, pain, oedema and heat, are observed in three out of four patients, but in the early phase, these are not easily distinguishable from less severe skin infections (5, 9). Erythema may be well-defined or diffuse, depending on the infection's portal of entry. Oedema is an early sign and precedes erythema, but is often overlooked.

Rapid symptom development should raise suspicion of NSTI, as should disproportionately severe pain in the soft tissue, especially if it extends beyond the areas with erythema. Purple or black discoloration, haemorrhagic bullae and crepitation are late-stage signs, while tissue necrosis and hypoesthesia occur even later (4, 15). Organ failure is common, and septic shock develops in

approximately 50 % of patients and up to 65 % of those with *S. pyogenes* infection (2, 4, 10). Relevant differential diagnoses are erysipelas, cellulitis, phlegmon, abscess, septic arthritis, postoperative wound infection and deep vein thrombosis.

Diagnosis

NSTIs are difficult to identify at an early stage, and up to 70 % of patients are initially misdiagnosed (15). Exploratory surgery is required to establish a diagnosis. Perioperative findings include loosening of skin, necrosis of subcutaneous tissue, discoloured or necrotic fascia and/or musculature, thrombosis of superficial veins, decomposed tissue without detectable anatomical boundaries, discoloured oedema fluid ('dishwater') and, usually, absence of pus (15, 16). These findings may be absent in the early stages, and repeated wound inspection and re-exploration are often necessary (2, 17). Figures 2a and 2b show a patient with NSTI in an upper extremity, pre- and perioperatively, illustrating the discordance between external signs and the extent of surgical treatment needed.

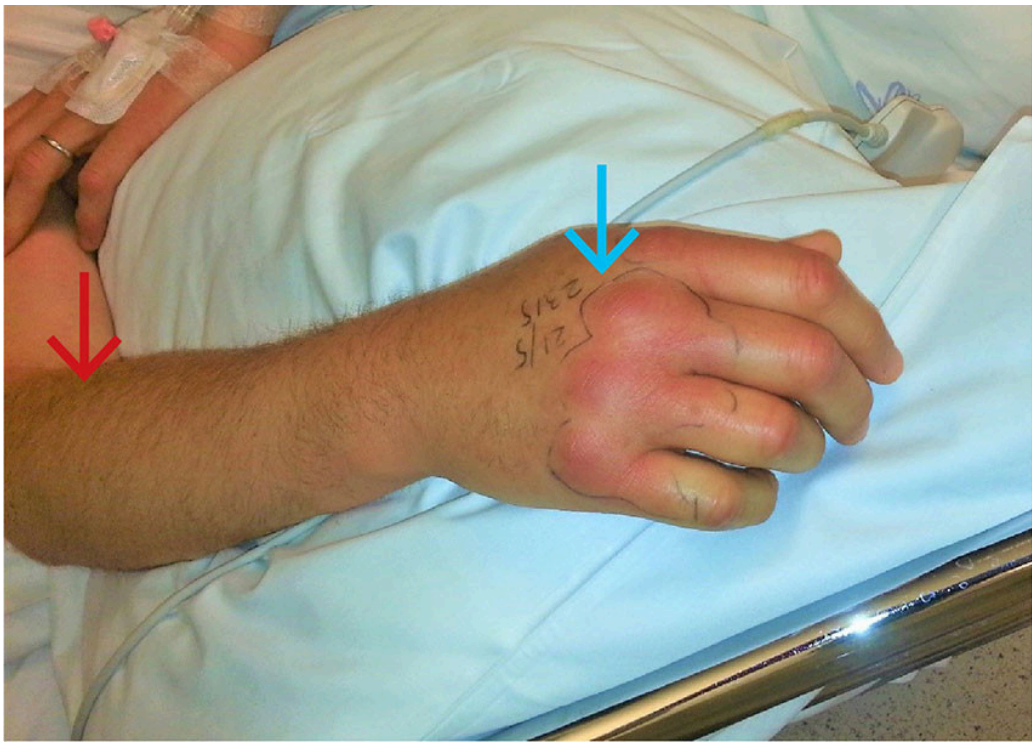

Figure 2a Patient with NSTI in the right upper extremity with S. pyogenes, clearly demarcated erythema and oedema on the dorsal side of the hand, marked with the date and time (blue arrow) to assess the progression of skin changes. The upper limit of the painful area was proximal to the forearm (red arrow).

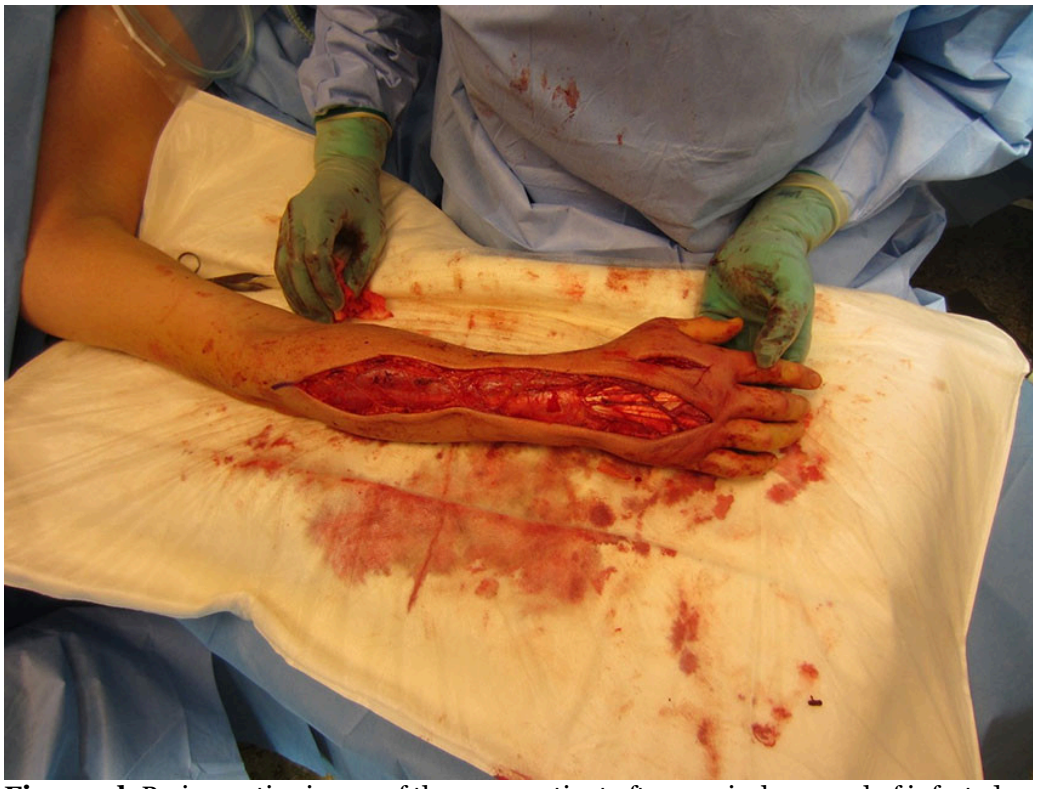

Figure 2b Perioperative image of the same patient after surgical removal of infected and avascular tissue up to several centimetres proximal to the erythema.

Rapid and precise bacteriological diagnosis is crucial for choosing the right antibiotics. Findings of bacteria on microscopic examination of a Gram stain from a normally sterile area strengthen the diagnosis, while negative microscopy does not rule it out. Cultures from normally sterile tissue are very often positive, but the accuracy of these culture results is dependent on proper sampling techniques and the use of correct materials (10).

Upon admission to the emergency department, blood gas, pre-transfusion tests and two sets of blood cultures are taken. Approximately 40 % of blood cultures are positive (4). Standard blood tests show the same pattern as in other serious infections. The LRINEC (Laboratory Risk Indicator for Necrotising Fasciitis) score is based on six biochemical blood test analytes (CRP, leukocytes, haemoglobin, sodium, creatinine and glucose) and is intended to distinguish NSTIs from non-necrotising skin and soft tissue infections (18). However, the score has shown low sensitivity and specificity in several studies, which advise against making decisions based solely on the scoring system in suspected NSTI, a position we support (16).

In the INFECT study, we found little practical benefit in leukocyte and CRP tests, while thrombomodulin, interleukin-1β, tumour necrosis factor-α and CXCL8 (interleukin-8) were shown to be promising biomarkers, but these findings have not been validated (11, 19). CT and MRI may be useful preoperatively to assess the extent of infection in surgically challenging anatomical areas, such as the head and neck region, but must not delay surgical treatment (5). Ultrasound can be useful, but this modality depends on the depth of infection and is also highly dependent on the operator (2). Due to the

low diagnostic precision and interrater reliability in microscopy, we do not recommend perioperative tissue sampling for histology as a diagnostic method (5, 9, 20).

Treatment

Only two randomised clinical trials have been carried out for NSTIs (21, 22). Consequently, guidelines are mainly based on clinical experience, retrospective studies, clinical trials for less severe skin and soft tissue infections, as well as knowledge of microbial aetiology and antibiotic efficacy.

Treatment requires a multidisciplinary approach. Efforts are made to control the infection through rapid surgical removal of devitalised tissue, and targeted antibiotic treatment is crucial for survival and outcome (9, 13). All patients with rapidly progressing severe soft tissue infection should undergo surgery without delay for diagnostic assessment, evaluation of infection spread and microbiological sampling.

The threshold for surgical exploration should be low, and we consider the reported 20 % rate of negative exploration to be acceptable (17). Both in the case of confirmed NSTI and in cases of doubt, re-exploration should be performed within 24 hours to ensure source control or to reassess the diagnosis (2, 17). The explored area should be inspected and revised daily until necrotic tissue is no longer detected. Radical surgery is crucial for reducing mortality but may result in extensive skin and tissue loss. This often necessitates skin grafting, reconstruction and rehabilitation to ensure functionality, limit negative aesthetic consequences and reduce chronic pain. There is therefore a strong emphasis on skin-sparing and limb-sparing surgical techniques.

The empirical antibiotic treatment in the national clinical guidelines for antibiotics in hospital settings is categorised by anatomical location (Figure 1) and tailored to Norwegian susceptibility patterns and current sepsis regimens (7). Beta-lactam antibiotics are the cornerstone of empirical treatment. Adjunct antibiotic therapy with clindamycin is initially recommended to inhibit potential toxin production and improve the effect on microbes in the stationary growth phase, primarily streptococci (23). For extremity infections, which are mainly monomicrobial, a combination of penicillin and clindamycin is recommended to treat streptococci and *Clostridium* spp. An aminoglycoside is also administered to ensure efficacy against *S. aureus* and Gram-negative rods (7). For infections in the head and neck region or abdominal and anogenital regions, piperacillin/tazobactam and clindamycin are recommended (7). Clindamycin can be discontinued if beta-haemolytic streptococci or *Clostridium* spp. are not found. If there is a risk of methicillin-resistant *Staphylococcus aureus* (MRSA), water-associated microbes, or bacteria that produce extended-spectrum beta-lactamases (ESBLs), refer to the national clinical guidelines for which antibiotics should be administered in particular situations (Figure 1) (4, 6, 7).

The antibiotic regimen should be adjusted according to culture findings and susceptibility patterns. Antibiotics are to be continued until further debridement is no longer necessary and there is clinical improvement with absence of fever for 48–72 hours (23). A retrospective study of antibiotic treatment +/– 7 days after source control showed no difference in mortality between the two groups (24).

Most patients require intensive care with mechanical ventilation and vasopressor therapy (4). Approximately 1/5 receive renal replacement therapy (3). Expected length of stay in intensive care is 5–12 days (4, 5).

Polyspecific intravenous immunoglobulin G (IVIG) neutralises soluble toxins produced by *S. pyogenes*. Few clinical studies have been conducted for IVIG as a treatment for NSTI, and the results are conflicting (22, 25). There is nevertheless some evidence that IVIG reduces mortality in cases of *S. pyogenes* infection (10, 25). The national clinical guidelines refer to an IVIG dosage regimen of 1 g/kg × 1 (day 1), followed by 0.5 g/kg × 1 (days 2 and 3) (7). However, experimental evidence shows that lower doses can yield a sufficient effect (26).

Studies of hyperbaric oxygen therapy have shown mixed results, but a recent meta-analysis has demonstrated a reduced risk of major amputations and hospital mortality (27). Guidelines give conflicting advice on the routine use of hyperbaric oxygen therapy and the choice of treatment protocol (2, 23).

Complications and prognosis

Even with the best treatment, the mortality rate for NSTI is around 20–30 %. The correlation between early surgery and survival is well documented (2, 13). Removal of necrotic tissue is lifesaving, but tissue loss is often extensive, with amputation performed in 10–20 % of cases (4, 5). Follow-up studies have shown that patients score lower on quality of life, and depression and PTSD rates are higher among survivors than the reference population (28).

Future perspectives and discussion

Treatment outcomes are still unsatisfactory for NSTIs. Rapid assessment and appropriate treatment are crucial for this patient group. Clear diagnostic criteria are needed to improve diagnosis and evaluation of outcomes and to develop clinical trials. Identifying promising biomarkers for necrosis and microbial aetiology could lead to faster and more targeted treatment (11). We have identified a need for interdisciplinary collaboration in developing national guidelines for addressing NSTIs beyond current antibiotic guidelines, to encompass the evaluation of contentious treatments and the centralisation of treatment options.

Furthermore, there is an unmet need for clinical trials, particularly for streptococcal infections, where there is a potential for targeted therapy. Randomised trials are particularly relevant for controversial modalities such as

IVIG and hyperbaric oxygen therapy (5, 27). The incidence of invasive *S. pyogenes* infection increased in 2023 and is a reminder of the need for continuous awareness of NSTIs among doctors and in society at large (1). Our research group seeks to devise a national, randomised clinical trial with immunoblocking in streptococcal infection, but collaboration is needed to accomplish this.

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The patient has consented to publication of the photographs in this article.

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